Association of secundum atrial septal defect with abnormalities of atrioventricular conduction or left axis deviation

Genetic study of 10 families

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A genetic analysis was made of 10 families in which the probands had a secundum atrial septal defect associated with abnormal atrioventricular conduction (first, second, or third degree heart block) or unexplained left axis deviation or a combination of these conduction disturbances. Diagnostic information was available on 51 (81%) of the first degree relatives. Three of the families appeared to be examples of a new syndrome which, with variable expression, was inherited as a non-sex-linked autosomal dominant. The main features were a secundum atrial septal defect; disease of the conducting tissue, which in some cases was progressive; unexplained left axis deviation; and unexpected death. These families did not seem to be examples of the Holt-Oram syndrome, for the upper limbs were clinically and radiologically normal in the 19 members examined.

The importance of recognizing this syndrome is the occurrence of progressive disease of the conducting tissue and the risk of sudden death. When, therefore, unexplained left axis deviation or prolonged atrioventricular conduction is found in association with a secundum atrial septal defect all available relatives should be examined.

In the remaining seven families there was only one affected first degree relative out of 39 examined. He was the son of one of the probands and had paroxysmal coronary sinus rhythm with an intact atrial septum.

Defects of the atrial septum, like other forms of isolated congenital heart disease, are usually examples of multifactorial aetiology (Nora, McNamara, and Fraser, 1967). The relative importance of genetic and environmental factors varies according to the anatomical types of congenital heart disease. This can be shown by using Falconer's (1965/1966) method of analysis, which enables genetic influences to be quantitated and expressed in terms of heritability. When applied to defects of the atrial septum heritability in secundum defects was 70 per cent compared with 45 per cent in atrioventricular defects (Emanuel, 1970).

Uncomplicated secundum atrial septal defects may occur in several members of the same family (Campbell, 1949; Carleton, Abelman, and Hancock, 1958; Davidsen, 1958; Howitt, 1961; Weil and Allenstein, 1961; Zuckerman *et al.*, 1962; Ehlers and Engle, 1966; Kahler *et al.*, 1966; Amarasingham and Fleming, 1967; Nora *et al.*, 1967;

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Campbell and Polani, 1961; Bizarro *et al.*, 1970; Zetterqvist *et al.*, 1971) and a dominant mode of inheritance has been suggested (Zuckerman *et al.*, 1962; Campbell and Polani, 1961; Zetterqvist *et al.*, 1971). When secundum atrial septal defects are associated with skeletal deformities of the upper limbs and dysrhythmias, as in the Holt-Oram syndrome (1960), inheritance is certainly dominant. More recently Björnstad (1974) suggested a dominant inheritance in patients with secundum atrial septal defect associated with prolonged atrioventricular conduction. He reported one such family and cited a further six from the literature (Howitt, 1961; Weil and Allenstein, 1961; Kahler *et al.*, 1966; Amarasingham and Fleming, 1967; Bizarro *et al.*, 1970).

Conversely, other conduction disturbances such as prolonged QT interval, bundle-branch block, bifascicular block, and complete heart block may, in the absence of an atrial septal defect, be familial and transmitted as a dominant characteristic (Mosetti, 1954; Trivella and Chella, 1960; Garza *et al.*,

1970; Simonsen and Madsen, 1970; Mathews, Blount, and Townsend, 1972; Husson *et al.*, 1973; Schaal *et al.*, 1973; Morgans, Gray, and Robb, 1974; Esscher, Hardell, and Michaëlsson, 1975).

This complex background prompted us to study a series of families in which the propositus had a secundum atrial septal defect associated with abnormal atrioventricular conduction or unexplained left axis deviation, or a combination of these.

Subjects and methods

Propositi were sought in whom a secundum atrial septal defect was present together with unexplained left axis deviation and/or abnormal atrioventricular conduction (first, second, or third degree heart block). Ten were found. Two of them were patients at the National Heart Hospital with secundum atrial septal defects, one with unexplained left axis deviation and the other with progressive disease of the conducting tissue which eventually required an artificial pacemaker. The other eight propositi were found among a consecutive series of 380

TABLE Clinical and electrocardiographic details of 10 propositi and 12 affected relatives

1 Family and Pedigree No.	2 Type of heart disease	3 ASD type and size (cm)	4 Additional abnormalities	5 Diagnosis confirmed	6 Electrocardiogram		8 Axis	9 Conduction
					Rhythm	PR		
↗ A III 7	ASD	FO 6.0 × 4.0	MR, cong.	A, S	SVT ↓ AF+CHB	—	+ 120	LBBB
A IV 1	ASD	—	MR	C, No PM	SR	0.28 ↓ 0.36	- 50	PRBBB
A IV 3	ASD	S ven. 6.0-7.0 × 3.0-4.0	No APV	S	PHB + NR	0.40 ↓ 0.56	N	N
A V 3	ASD	—	—	Cl	SR	0.16	N	PRBBB
↗ B III 3	ASD	—	—	C, A	SR	0.20	- 45	PRBBB
B IV 5	ASD	—	MVD (C)	C, A	SR	0.22	N	PRBBB
B IV 6	ASD	—	—	C, A	SR ↓ PHB	0.20 ↓ 0.28	N	N
C I 3	?CHD	—	—	Cl No PM	—	—	—	—
C II 3	ASD	—	—	Cl No PM	—	—	—	—
C II 4	CHD	—	—	Cl No PM	—	—	—	—
C III 1	CHD	—	—	Cl No PM	—	—	—	—
↗ C III 2	ASD	FO 6.0 × 2.0	LSVC, MR, cong.	S & PM	AF	—	- 45	PRBBB
C IV 1	ASD	IVC 4.0 × 3.0	—	S	SR	0.20	- 25	PRBBB
C V 3	ASD	—	Hypospadias	C, A	SR	0.16	- 25	PRBBB
↗ D III 1	ASD	IVC 8.0 × 2.0	—	S	SR	0.32	- 10	PRBBB
↗ D IV 1	CD	—	—	Cl	CSR(P)	0.16	N	N
↗ E	ASD	IVC 6.0 × 4.0	—	S	SR	0.28	N	PRBBB
↗ *F	ASD	IVC 3.5 × 1.5	—	S	SR	0.13	- 112	RBBB
↗ G	ASD	IVC 8.0 × 5.0	MR, ? cong.	S & PM	SR	0.26	+ 125	RBBB
↗ H	ASD	FO 3.0 × 1.5	—	S & PM	SR	0.24	N	PRBBB
↗ †J	ASD	FO 5.0 × 3.0	LSVC	S	SR	0.13	- 150	PRBBB
↗ K	ASD	FO 3.5 × 1.5	—	S	SR	0.24	+ 100	PRBBB

* Two siblings with aortic valve disease (? congenital).

† Distant cousin with Fallot's tetralogy.

Abbreviations. Col. 1: ↗ = propositus. Col. 2: ASD = atrial septal defect; CHD = congenital heart disease of unknown type; CD = conduction defect. Col. 3: FO = fossa ovalis, IVC = inferior vena caval type of secundum atrial septal defect; S ven. = sinus venosus. Col. 4: MR = mitral regurgitation; MVD(C) = cleft mitral valve without mitral regurgitation; cong. = congenital; LSVC = left superior vena cava; APV = anomalous pulmonary veins. Col. 5: S = surgery; C = catheter; Cl = clinical examination only; A = left ventricular angiogram; PM = post mortem examination. Col. 6: SR = sinus rhythm; AF = atrial fibrillation; CHB = complete heart block; CSR(P) = paroxysmal coronary sinus rhythm; NR = nodal rhythm; PHB = partial heart block (1st and 2nd degree). Col. 8: N = normal; QRS axis. Col. 9: PRBBB = partial right bundle-branch block; RBBB = right bundle-branch block; LBBB = left bundle-branch block; N = normal.

patients who had had a secundum atrial septal defect closed at The Middlesex Hospital. The conduction defects in these eight probands included prolonged atrioventricular conduction exceeding 0.22 s in five, one of whom also had left axis deviation; two had isolated left axis deviation, and one an intermediate axis. Clinical and electrocardiographic details of the probands are shown in the Table.

The genetic study was confined to these 10 families.

As in previous studies (Emanuel *et al.*, 1968; Emanuel, Withers, and O'Brien, 1971), the general practitioner of the proband was contacted and then an explanatory letter requesting an interview was sent to each family. The proband or a close relative was seen, at home whenever possible, and at the interview a pedigree was

drawn up which included first and second degree relatives and first cousins.

All first degree relatives who were willing to co-operate were asked to attend the National Heart Hospital, The Middlesex Hospital, or a convenient regional hospital, where they were examined clinically and had an electrocardiogram and chest radiograph. When an atrial septal defect or a conduction defect, or both, was found in any first degree relative the study in that particular family was extended to include second degree and more distant relatives. All relatives in these families, of whatever degree, were asked for radiographs of their elbows, forearms, wrist, and hands to exclude skeletal deformities of the upper limbs.

The clinical details and electrocardiograms were

assessed by one of us (R.E.) and the radiographs were analysed independently (K.J.). Information on relatives who had died was sought from hospital notes, general practitioner reports, necropsy reports, and death certificates.

Results

In the 10 families available for genetic analysis there were 63 first degree relatives (20 parents, 27 siblings, and 16 children). Forty-six of the 50 living first degree relatives had clinical examinations, electrocardiograms, and chest radiographs. Adequate diagnostic information was obtained on five of the 13 first degree relatives who had died. Thus information was available on 51 (81%) of the first degree relatives.

In the 4 families (A, B, C, and D; see Fig.) where one or more of the first degree relatives were found to have an atrial septal defect or a conduction defect, or both, 15 more distant relatives also were examined as above, and adequate diagnostic information was obtained on three who had died.

In three families (A, B, and C) one or more of the relatives had some form of congenital heart disease, and a total of 14 members were affected. Nine had a proved secundum atrial septal defect, though in one of these (AV₃) confirmatory evidence was confined to the electrocardiogram and chest radiograph. In another member with left axis deviation the atrial septal defect was confirmed by cardiac catheterization but there was no left ventriculogram, so an atrioventricular defect could not be excluded; in another the diagnosis of atrial septal defect was made on clinical grounds alone; and in the remaining three the congenital heart disease was of unknown type. In eight of those (nine) with proved atrial septal defects (which included the patient without left ventriculogram) there were additional conduction abnormalities which included unexplained left axis deviation in five, one of whom had prolonged atrioventricular conduction, and progressive disease of the conducting tissue in four. Mitral valve abnormalities, thought to be congenital, were found in three of the cases of proved secundum atrial septal defect and also in the case where the type of atrial defect was uncertain. In one patient with severe mitral regurgitation the valve was inspected at surgery and necropsy. In two others the mitral valve abnormalities were diagnosed from the left ventriculogram, and in the fourth, who had neither a left ventriculogram nor surgery, an apical pansystolic murmur was at times noted (Table).

The findings in the individual families were as follows. In family A there were four cases of secundum atrial septal defect in three generations. Three had associated conduction defects, and in all

three the disease of the conducting tissue was progressive. The propositus also had moderate mitral regurgitation from a prolapsing posterior cusp seen on the left ventriculogram. One member of this family died suddenly aged 23 years. She had an atrial septal defect (type unknown), left axis deviation, progressive prolongation of the PR interval, and on occasions an apical pansystolic murmur was noted suggesting mitral regurgitation. Her sudden, unexpected death may have been related to disease of the conducting tissue.

In family B the propositus had a secundum atrial septal defect with left axis deviation. Both her children had small secundum atrial septal defects. In one there was angiocardigraphic evidence of a cleft mitral valve without regurgitation and in the other there was progressive disease of the conducting tissue.

In family C there were six, possibly seven, cases of congenital heart disease in five generations. Three had proved secundum atrial septal defects, all with unexplained left axis; in addition one of them had an abnormal mitral valve. At surgery, and subsequently at necropsy, the cusps were found to be thin with nodular edges and elongated chordae. There was no evidence of rheumatic heart disease but the valve was not examined histologically. In this family there were two cases of unexpected death among the relatives with congenital heart disease of unknown type; both were girls, aged 14 and 19 years.

In one family (D) the son of the propositus had paroxysmal coronary sinus rhythm with an intact atrial septum.

Out of the 34 living members of the above four families (A, B, C, and D) examined, 27 had their elbows, forearms, wrists, and hands radiographed and no skeletal abnormality was found.

In the remaining six families (E, F, G, H, J, and K) there was no instance of atrial septal defect or conduction defect. In family F, however, two siblings of the propositus had aortic valve disease with stenosis and regurgitation which could have been congenital, as neither had a rheumatic history, and in family J a distant cousin had Fallot's tetralogy.

Clinical and electrocardiographic details of the propositi and the affected relatives are given in the Table.

The incidence of unexplained left axis and prolonged atrioventricular conduction associated with secundum atrial septal defect was established by analysing the electrocardiograms of 380 consecutive patients who had had their septal defects closed at The Middlesex Hospital. Of the original eight propositi from this source two were excluded from

this part of the analysis, one because of an intermediate axis of -150° and the other because she was the proposita of one of the families (C) with the autosomal dominant syndrome. Thus there were six cases out of 378 (1.6%) with one of the conduction disturbances mentioned above. Left axis occurred in two (0.5%) and one of these had prolonged atrioventricular conduction, and a prolonged atrioventricular conduction with normal axis occurred in the remaining four (1.1%).

Discussion

Three of the families (A, B, and C) were of particular interest for they appeared to represent a previously unreported syndrome which, with variable expression, was inherited as a non-sex-linked autosomal dominant. The Holt-Oram syndrome did not appear to be implicated, for clinical and radiological examination of the upper limbs were normal in the 19 relatives studied. Deformed little fingers were reported in the propositus of family C and her twin sister, but both had died before this study was undertaken and no radiographs were available. Thus the salient features of this syndrome were a secundum atrial septal defect, disease of the conduction tissue, in some cases progressive, and unexpected death.

These three families contained four members with progressive disease of the conducting tissue. In one (A III 7), a man of 51 years when first seen, the electrocardiogram showed a supraventricular tachycardia with varying atrioventricular block, a mean QRS axis of $+120^\circ$, and a bizarre left bundle-branch block. Atrial activity became less evident on subsequent electrocardiograms, and nine years after his secundum atrial septal defect had been closed he developed syncopal attacks due to complete heart block and atrial fibrillation with a ventricular rate between 30 and 36/min and required pacing. His daughter (A IV 1) was known to have an atrial septal defect (type uncertain, no left ventriculogram). Her electrocardiogram showed left axis deviation (-50°) and progressive prolongation of the PR interval from 0.28 s to 0.36 s. Her sudden unexpected death at the age of 23 years may have been due to progressive disease of the conduction tissue. Her sibling (A IV 3), with a proved secundum atrial septal defect, had had abnormal atrioventricular conduction with progressive lengthening of the PR interval from 0.40 s to 0.56 s. He now has second degree heart block (Mobitz type 1) and paroxysmal nodal rhythm.

Another case of increasing atrioventricular conduction occurred in family B. A boy (B IV 6), who had been under observation since birth, always had a slightly prolonged PR interval for a child (0.20 s) but this was stable until the age of 6½ years. The

PR interval then became progressively longer and by the age of 10 years was 0.28 s. The following year he developed dizzy attacks and was found to have second degree heart block (Mobitz type 1). The His electrogram confirmed disease of the atrioventricular node with an AH time of 210 ms which, after atropine, shortened only to 160 ms. His mother (B III 3), who had been under observation for 14 years, had a stable PR interval of 0.20 s but probably had disease of the atrioventricular node, as the His electrogram shows an AH interval of 147 ms.

Data from these cases are compatible with progressive disease or degeneration of the conducting tissue, and its distribution in family A, and possibly family B, where two generations were involved, suggests this feature can be inherited as a dominant characteristic.

Though congenital abnormalities of the mitral valve were present in four members of the three families, A, B, and C (Table), these findings are of doubtful significance since such abnormalities, with or without regurgitation, are not uncommon in isolated cases of secundum atrial septal defect (McDonald *et al.*, 1971; Goodman and Hancock, 1973; Hynes *et al.*, 1974; Victorica, Elliott, and Gessner, 1974). The incidence of valve abnormalities in the 10 families is not known, partly because none of the clinically normal relatives was examined by angiocardiology or echocardiography, and partly because, of the 18 patients with a secundum atrial septal defect, 10 of the 11 treated surgically had their defect closed using hypothermia by surface cooling, so inspection of the mitral valve was almost certainly inadequate, and four had neither left ventriculography nor surgery.

Left axis deviation associated with secundum atrial septal defects has been noted previously (Somerville, 1961). The presence of additional coronary artery disease, hypertension, or a ventricular septal defect was thought to be the explanation of this unusual finding, but in the five cases encountered in families A, B, and C (Table) this does not seem to be the explanation. The presence of hypertension and ventricular septal defects was excluded, and, as the average age of these patients was 25.6 years (range 5–48 years) and four of the five were female, coronary artery disease seems unlikely. We suggest that in these families (A, B, and C) the left axis deviation was genetically determined and an integral part of the autosomal syndrome.

In this study, in addition to families A, B, and C, we encountered two other cases of unexplained left axis deviation – the propositus in family D, a man aged 23 years who also had prolonged atrioventricular conduction, and the propositus in family F, a

man aged 34. We have no certain explanation for the axis deviation in either but once again suspect it may be genetically determined, for in family D the son of the propositus had paroxysmal coronary sinus rhythm, and in family F two siblings of the propositus had aortic valve disease which could have been congenital as there was no rheumatic history.

Our data did not support Björnstad's (1974) suggestion that where a secundum atrial septal defect occurred with prolonged atrioventricular conduction both were inherited as an autosomal dominant. Five of our propositi (families D, E, G, H, and K) had a PR interval exceeding 0.22 s, and in only one of these families was there an affected relative. This was in family D, where the son of the propositus had paroxysmal coronary sinus rhythm with an intact atrial septum and, when in sinus rhythm, normal atrioventricular conduction.

Of the 10 families analysed, three (A, B, and C) appear to represent a previously undescribed autosomal, non-sex-linked dominant syndrome which, with variable expression, features secundum atrial septal defect, progressive disease of the conducting tissue, sudden death, and, possibly, congenital abnormalities of the mitral valve. The importance of recognizing this syndrome lies in the uncertainty of the prognosis and the risk of sudden death, which is probably due to disease of the conducting tissue. When, therefore, a secundum atrial septal defect is associated with any conduction abnormality, particularly unexplained left axis deviation with or without prolonged atrioventricular conduction, a careful family history and examination of all available relatives is indicated.

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Appendix

Case reports

The appendix contains the medical and surgical details of the four families (A, B, C, and D; see Fig.) in which one or more members other than the propositus were affected. Details of the remaining six propositi (E, F, G, H, J, and K) without an affected relative are shown in the Table.

Family A: Four affected members in three generations

- A I 2.* – Died aged 71, cerebral thrombosis, myocarditis.
- A I 4.* – Died old age.
- A II 6.* – Died aged 68, cancer of bowel.
- A II 7.* – Died aged 78, cancer.
- A III 6.* – Died aged 8, meningitis.
- A III 7.* – Male, born 10 September 1908. Murmur heard age 10. Remained asymptomatic until aged 47, then noted progressive effort dyspnoea and developed cardiac failure aged 51 years. Clinical signs of atrial septal defect. Electrocardiogram: supraventricular tachycardia with varying atrioventricular block, right axis $+120^\circ$, with left bundle-branch block. Cardiac catheterization abandoned owing to onset of ventricular tachycardia. At operation (28 March 1960) a fossa ovalis secundum atrial septal defect 6×4 cm was closed. Remained well until 1966 when a small cerebral embolus caused a right hemiparesis: complete recovery. In 1967 he noted increased effort dyspnoea. Reinvestigation showed moderate mitral regurgitation from a ballooning posterior cusp. In January 1969 he had further increase in dyspnoea and three syncopal attacks with loss of consciousness lasting up to 10 min. Electrocardiogram at that time showed atrial fibrillation, complete heart block, and ventricular ectopics with an irregular ventricular rate 30–36/min. Pacemaker inserted. Pacemaker changes have been required in May 1969, March 1971, and October 1973.
- A IV 1.* – Female, born 22 August 1937. Asymptomatic murmur noted age 12 at routine school examination. Physical signs of atrial septal defect. At times an apical pansystolic murmur was noted suggesting mitral regurgitation. Atrial septal defect confirmed by cardiac catheterization in March 1957, which showed a left to right shunt at atrial level with a pulmonary/systemic

flow ratio of 3:1. No left ventricular angiogram. Electrocardiogram showed sinus rhythm, left axis -50° , partial right bundle-branch block, QRS 0.1 s, PR progressive lengthening from 0.28 s to 0.36 s. In 1960, aged 23, the patient died suddenly while eating breakfast. No post-mortem examination. Therefore an atrioventricular defect cannot be excluded.

A IV 3. – Male, born 30 August 1946. Asymptomatic. Atrial septal defect diagnosed in 1967 during an earlier family study. Serial electrocardiograms showed progressive disease of the conducting tissue including first degree heart block with the PR increasing from 0.40 s to 0.56 s, second degree heart block (Mobitz type 1), nodal rhythm and periods of atrioventricular dissociation. The axis was normal and the QRS 0.08 s. Cardiac catheterization in April 1967 confirmed a left to right shunt at atrial level with a pulmonary/systemic flow ratio of 2:1. At operation in May 1967 a sinus venosus secundum atrial septal defect was found without anomalous veins from the right lung. The rest of the septum was aneurysmal and thin. During the operation it ruptured giving a total defect of $6-7 \times 3-4$ cm.

A V 3. – Male, born 3 September 1972. Murmur noted at clinic age 1 year. Clinical and radiological signs are those of a moderate sized atrial septal defect. Not yet investigated in view of age and clinical well-being. Electrocardiogram showed PR 0.16 s, normal axis, partial right bundle branch block, QRS 0.08 s.

Family B: Three affected members in two generations

- B I 1.* – Died aged 73, cancer of stomach.
- B I 2.* – Died aged 91, old age.
- B I 3.* – Died aged 84.
- B II 2.* – Depressed sternum, otherwise normal.
- B II 3.* – Died aged 59, cancer of uterus.
- B III 3.* – Female, born 13 March 1946. Murmur noted age 3, has remained asymptomatic. Physical signs typical of atrial septal defect without evidence of mitral regurgitation. Cardiac catheterization May 1963 confirmed a left to right shunt at atrial level with 3.6:1 pulmonary/systemic flow ratio. The pulmonary artery pressure was normal. Left ventriculography in September 1967 showed normal left ventricular outflow, confirming a secundum atrial septal defect. The His electrogram suggested disease of atrioventricular node with an AH interval of 147 ms. Other measurements were normal: PA 38 ms, HV 48 ms. Electrocardiogram showed sinus rhythm, left axis -45° , partial right bundle-branch block, QRS 0.12 s, PR 0.20 s.
- B IV 5.* – Female, born 1 January 1961. Murmur noted age 2 months. Remained asymptomatic except for repeated respiratory tract infections. Cardiac catheterization on 25 May 1964 confirmed small left to right shunt at atrial level; appearance of left ventriculogram consistent with a secundum atrial septal defect and a cleft anterior cusp of mitral valve. Lateral view showed an irregularity in the contour of the anterior wall of the left ventricular outflow tract. No mitral regurgitation demonstrated. Electrocardiogram showed sinus rhythm, normal axis, partial right bundle-branch block, QRS

0.1 s, PR 0.22 s. Thought to be no indication for closing the small atrial septal defect.

B IV 6. Male, born 31 May 1962. Murmur noted aged 6 weeks. Remained well except for frequent chest infections. Cardiac catheterization June 1969 confirmed small left to right shunt at atrial level with a pulmonary/systemic flow ratio of 1.5:1. Left ventriculogram normal. Atrioventricular conduction was always slightly prolonged, with PR interval of 0.20 s, but stable. From the age of 6½ years there was progressive lengthening of the PR interval (age 6½ PR 0.24 s, age 8 PR 0.26 s, age 9 PR 0.26 s, age 10 PR 0.28 s. Measurements made with heart rates between 80 and 100/min). He remained asymptomatic until aged 11 and then developed dizzy attacks. Once his mother noted a bradycardia of 40/min, which lasted for 24 hours. Electrocardiograms at this time showed second degree heart block (Mobitz type 1). The His electrogram showed disease of the atrioventricular node with AH time of 210 ms, HV 35 ms, PA 40 ms. After atropine 0.6 mg i.v., AH 160 ms, HV 35 ms, and PA 30 ms. He is now being treated with anticholinergic therapy, though it is expected he will eventually need a pacemaker because of the progressive disease of conducting tissue.

Family C: Seven affected members in five generations

C I 3. – Male, date of birth unknown. Died with 'heart trouble' aged 33.

C II 2. – Died aged 70 after accident.

C II 3. – Female, born 25 June 1891. Known to have had heart disease all her life but refused investigation. Aged 24 developed tachycardia after birth of twin daughters. Bedridden from age 38. General practitioner reported signs compatible with atrial septal defect. Died in heart failure aged 73.

C II 4. – Female, date of birth unknown. Said to have been a 'blue baby.' Died aged 19 years.

C III 1. – Female, born 28 October 1915. Twin of propositus. Known to have congenital heart disease, with deformed little fingers. Died aged 14 years. No necropsy.

C III 2. – Female, born 28 October 1915. Murmur noted at routine examination aged 8 years. Palpitation during first pregnancy aged 29. Onset of atrial flutter with effort dyspnoea aged 35. Atrial septal defect diagnosed. Had abnormality of both little fingers, said to be similar to twin sister, but no clinical details or radiographs available. Cardiac catheterization confirmed left to right shunt at atrial level with a pulmonary/systemic flow ratio of 2.4:1. Fossa ovalis secundum atrial septal defect measuring 2 × 6 cm closed at operation in Jan-

uary 1963: mitral valve found to be nodular and regurgitant. The lesion was thought to be congenital. There was also a left superior vena cava. The patient died after the operation. Electrocardiogram showed atrial fibrillation, left axis –45°, incomplete right bundle-branch block, QRS 0.12 s.

C IV 1. – Female, born 19 December 1944. Murmur first noted aged 5 years when she had pneumonia, otherwise asymptomatic. Cardiac catheterization confirmed left to right shunt at atrial level. Pulmonary/systemic blood flow 3:1. At operation in October 1963 an inferior vena caval type of secundum atrial septal defect measuring 4 × 3 cm was closed. Mitral valve normal. Electrocardiogram showed sinus rhythm, left axis –25°, partial right bundle-branch block, QRS 0.1 s, PR 0.20 s.

C V 3. – Male, born 2 October 1968. Murmur noted shortly after birth when examined for hypospadias. No cardiac symptoms. Signs compatible with small atrial septal defect. Cardiac catheterization and left ventriculography (September 1973) confirmed small secundum atrial septal defect with pulmonary/systemic flow ratio of 1.4:1. Electrocardiogram showed sinus rhythm, left axis –25°, partial right bundle-branch block, QRS 0.08 s, PR 0.16 s. In view of the size of the defect surgery was not advised.

Family D: Two affected members in two generations

D I 1. – Died aged 84.

D I 2. – Died aged 70, cerebral haemorrhage.

D I 3. – Died aged 78.

D I 4. – Died aged 80.

D II 7. – Died aged one month, no necropsy.

D II 10–15. – All died aged over 65.

D III 1. – Male, born 20 September 1932. Atrial septal defect diagnosed aged 18 after routine chest radiograph. Cardiac catheterization confirmed left to right shunt at atrial level with a pulmonary/systemic flow ratio of 2.3:1. At operation in June 1956 large fossa ovalis secundum atrial septal defect 8 × 2 cm extending into the inferior vena cava was closed. Electrocardiogram showed sinus rhythm, left axis –10°, minor degree of intraventricular block, PR 0.32 s.

D III 2. – Died aged one month, bronchopneumonia and enteritis.

D IV 1. – Male, born 4 March 1958. Asymptomatic. Normal physical findings and chest radiograph. Abnormal electrocardiogram noted during this study. Paroxysmal coronary sinus rhythm, normal axis. QRS 0.08 s, PR 0.16 s.